Chronic beta-blocker therapy improves outcome and reduces treatment costs in chronic type B aortic dissection

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Abstract: OBJECTIVES To compare the medical treatment of chronic type B aortic dissection with beta-blockers versus other antihypertensive treatments in terms of their requirement for surgical intervention and treatment costs. METHODS Case records of the 130 patients treated for aortic dissection type B in this unit between 1988 and 1997 were reviewed. Seventy-eight of 130 patients with chronic dissection have received isolated medical treatment. Seventy-one of 78 patients were discharged alive. Fifty-one of 71 received beta-blocker treatment, 20/71 were treated with other antihypertensive drugs. RESULTS Surgery for aortic dissection became necessary in 20/71 patients (28%) during follow-up (mean, 4.2 years): 10/51 in the beta-blocker group and 9/20 in the other antihypertensive drug group. The freedom from subsequent aortic operation was 80 and 47%, respectively (P=0.001). Indications for emergency surgery were increased aortic diameter (79%), symptomatic aortic aneurysm (11%), and renal artery hypoperfusion (5%). The median hospitalization time during follow-up (dissection-related) was 2 days for patients who received beta-blockers and 16 days for patients who received other antihypertensive drug treatments (P=0.001). The cost of treatment/patient per year amounted to 644 and 12748 euros, respectively. CONCLUSIONS A substantial proportion of patients with chronic type B dissection who receive initial medical management will later need surgery. Long-term treatment with beta-blockers reduces the progression of aortic dilatation, the incidence of subsequent hospital admissions, as well as the incidence of late dissection-related aortic procedures and the cost of treatment. Patients with chronic type B dissection need, in addition to frequent follow-up of aortic diameter, continuous treatment with beta-blocking agents.

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Chronic β-blocker therapy improves outcome and reduces treatment costs in chronic type B aortic dissection ☆

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Abstract

Objectives: To compare the medical treatment of chronic type B aortic dissection with β-blockers versus other antihypertensive treatments in terms of their requirement for surgical intervention and treatment costs. **Methods**: Case records of the 130 patients treated for aortic dissection type B in this unit between 1988 and 1997 were reviewed. Seventy-eight of 130 patients with chronic dissection have received isolated medical treatment. Seventy-one of 78 patients were discharged alive. Fifty-one of 71 received β-blocker treatment, 20/71 were treated with other antihypertensive drugs. **Results**: Surgery for aortic dissection became necessary in 20/71 patients (28%) during follow-up (mean, 4.2 years): 10/51 in the β-blocker group and 9/20 in the other antihypertensive drug group. The freedom from subsequent aortic operation was 80 and 47%, respectively ($P = 0.001$). Indications for emergency surgery were increased aortic diameter (79%), symptomatic aortic aneurysm (11%), and renal artery hypoperfusion (5%). The median hospitalization time during follow-up (dissection-related) was 2 days for patients who received β-blockers and 16 days for patients who received other antihypertensive drug treatments ($P = 0.001$). The cost of treatment/patient per year amounted to 644 and 12 748 euros, respectively. **Conclusions**: A substantial proportion of patients with chronic type B dissection who receive initial medical management will later need surgery. Long-term treatment with β-blockers reduces the progression of aortic dilatation, the incidence of subsequent hospital admissions, as well as the incidence of late dissection-related aortic procedures and the cost of treatment. Patients with chronic type B dissection need, in addition to frequent follow-up of aortic diameter, continuous treatment with β-blocking agents.

Keywords: Aortic dissection; Antihypertensive agent; Beta-blocker; Cost of treatment

1. Introduction

In contrast to Stanford classification type A dissections of the aorta, which are the most serious vascular catastrophe [1] and which carry an extremely high early mortality due to spontaneous rupture within the pericardium, type B dissections have a lower incidence of spontaneous rupture and tend to become chronic [2]. Nevertheless, a substantial proportion of patients with chronic type B dissections of the aorta will eventually require surgery because of progressive aortic dilatation. β-Blockers reduce the rate of rise (dP/dt) of the aortic pressure wave and may prevent or retard aortic dilatation [3–7] and reduce treatment costs.

2. Materials and methods

Between 1988 and 1997, 130 patients were treated for aortic dissection type B at the University Hospital Zurich. Twenty-six of 130 (20%) were female and 104/130 (80%) were male. The mean age at the time of the hospitalization for acute type B aortic dissection was 61 ± 11.2 years (range, 23–84 years). Fifty-two of 130 patients were treated surgically, 41 as emergency and 11 urgently before discharge. The indications for emergency surgery were: aortic rupture (39%); ischaemia of the aortic branches (34%); persistent pain (10%); aortic diameter of >6cm (7%); other indications (10%). The indications for urgent surgery (before hospital discharge) were: ischaemia of the aortic branches (36%); left pleural effusion (18%); increas-

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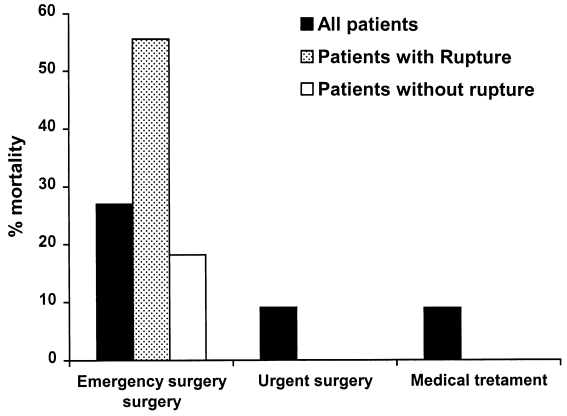

Fig. 1. In-hospital mortality aortic dissection type B. In-hospital mortality (%) for aortic type B aortic dissections by time of surgical intervention (emergency or urgent) and the treatment (medical treatment).

ing aortic diameter (18%); persistent pain (9%); other indications (19%).

In the absence of rupture or complications of the dissections, 78/130 patients received medical treatment alone; 71/78 of the medically treated patients were discharged alive. Of these, 51 received treatment with β-blockers and 20 were treated with other antihypertensive drugs. The mean age of the medically treated patients was 64 years (61.8 ± 8.9 years for patients who received β-blockers and 65.2 ± 12.6 years for patients who received other antihypertensive medication).

The records of all patients who were treated for type B aortic dissection were reviewed. There were no statistically significant differences between the group given β-blockers and the group given other antihypertensive medication with respect to the incidence of smoking (25 and 21%, respectively) and the incidence of obstructive airways disease (8.9 and 7.1%, respectively). The diameter of the aorta at the time of diagnosis also did not differ significantly between the group given β-blockers (<4.5 cm: 41 (80%); 4.5–5.5 cm: six (12%); >5.5 cm: four (8%)) and those given other antihypertensive medications (<4.5 cm: 15 (75%); 4.5–5.5 cm: three (15%); >5.5 cm: two (10%)). All patients who were still alive were contacted and asked to complete a questionnaire with the help of their doctor, in particular, CT-scan data was collected. The total follow-up period encompassed 194 years, with a mean observation time of 4.2 years (3.9 ± 3.2 years for the group given β-blockers and 4.3 ± 2.5 years for the group given other antihypertensive medications). A total of 19/130 (14.6%) patients died during the first hospitalization, and of the remaining 111 patients, follow-up was completed in 105 patients (95%); 37 patients died during follow-up.

The costs of treatment correspond to the those of the University Hospital, Zurich. The prices cover all hospital costs as follows: 1 day's stay in hospital, 1044 euros; 1 day's stay in an intensive care unit, 2680 euros; major aortic surgery, 9375 euros; 100 mg atenolol, 0.55 euros.

2.1. Statistical analysis

Variables are reported either as percentages or as means ± standard deviation. Statistical analyses were performed using SPSS 6.1 software. The effects on nominal variables were evaluated with the Chi-quadrant test and effects on independent variables were evaluated with the Mann–Whitney and Kruskal–Wallis tests; continuous variables were univariately evaluated with the Wilcoxon-signed rank test. Differences between groups were analyzed using the log-rank test. Significance was assumed at a P level of <0.05.

3. Results

Seventy-eight of 130 patients who were treated for type B dissection, in the absence of rupture or complications of the dissection, received medical treatment. The hospital mortality was 9% in medically treated patients compared with 9.1% for patients undergoing urgent surgery and 27% for those with emergency surgery (Fig. 1). Seventy-one of 78 of the medically treated patients were discharged alive. During follow-up, 51 patients received antihypertensive treatment with β-blockers and 20 patients received other antihypertensive drugs. During follow-up, 9/51 (18%) of the β-blocker-treated patients and 11/20 (55%) from the other treatment group needed dissection-related surgery ($P = 0.002$). Increasing diameter of the aorta was the most important indication for surgery in both groups (Table 1). The incidence of increasing aortic diameter was 12% (6/51) in the β-blocker group and 40% (8/20) in the other treatment group ($P = 0.002$). The freedom from subsequent aortic operation was 80 and 47%, respectively ($P = 0.001$; Fig. 2).

The median hospitalization during follow-up (related to dissection) was 2 days for patients treated with β-blockers and 16 days for patients treated with other antihypertensive drugs ($P = 0.001$). The cost of treatment/patient per year amounted to 644 and 12 748 euros ($P = 0.001$) for patients given β-blockers and other antihypertensive drugs, respectively.

Table 1
Indications for late surgery indications for late surgery in chronic type B dissection for the two therapeutic strategies: antihypertensive therapy with and without β-blocker

	β-blocker group	Other antihypertensives group
Aortic diameter	6	8
Persistent pain	2	1
Lower limb ischaemia	1	
Rupture		1
Visceral ischaemia		1

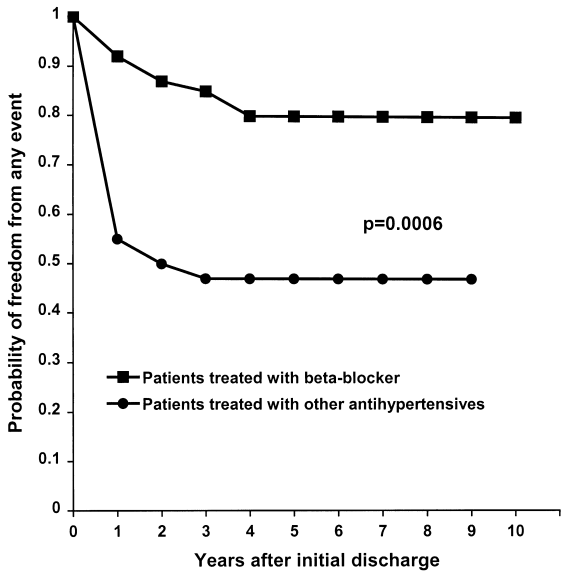

Fig. 2. Freedom from any event – chronic aortic dissection type B. Freedom from any event in patients with chronic type B aortic dissection, beginning from the discharge of the first hospitalization.

4. Discussion

Long-term treatment with β-blockers for chronic type B aortic dissection reduces the progression of aortic dilatation and the incidence of subsequent hospital admissions, as well as the incidence of late dissection-related aortic procedures and the cost of treatment.

It has been generally advocated that patients who have type B acute aortic dissection without complications, such as rupture, potential risk of rupture or organ ischaemia, should be treated with hypotensive drugs during the acute phase and that surgical treatment be carried out if the aortic diameter becomes enlarged during the chronic phase [8]. The goals of early medical treatment in the acute phase are to reduce blood pressure and heart rate, and to treat congestive heart failure [9]. Nevertheless, 11% of all patients treated in our institution for acute type B aortic dissection needed surgery after the acute phase but before discharge, most frequently because of an increase in aortic diameter.

The pharmacological approach is aimed primarily at the forces that influence dissection propagation, namely the pulsatile load (dP/dt) and blood pressure. Where luminal dilatation of the aorta occurs, shear stresses on the wall are greatly increased, according to the law of LaPlace, in which wall tension at a constant arterial pressure, increases with increasing luminal diameter [10]. Yin et al. have shown that dP/dt, which is also affected by wave reflections (conditions of increased peripheral vascular resistance), is greatest in areas of dilatation [11]. In cases of type B dissections, the portion of the aorta just distal to the left subclavian artery is subject to a significant degree of torsion and flexion during each cardiac circle. Experimental models of aortic dissection have shown that two interrelated forces of dP/dt and blood pressure play a part, not only in intimal tear formation, but also in the propagation of aortic dissection [1]. Studies using artificial aortas indicate that dissection propagation occurs when the dP/dt is high and the flow is pulsatile, not laminar or non-turbulent. Studies in hypertensive turkeys found that β-blockers, at doses that do not decrease the dP/dt, afford protection from aortic dissection [12]. Additional experimental evidence from dog models supports the role of blood pressure in the propagation of the aortic dissection; Carney et al. showed that the depression of myocardial contractility alone does not prevent progression of dissection, but that the inhibition of propagation can be achieved by controlled hypotension plus myocardial depression [13].

Theoretically, the use of β-blockers offers many potential benefits. The ability of β-adrenergic blockade to reduce pulsatile force (or dP/dt) has been demonstrated in animal models [14] and in patients with malignant hypertension [15]. Oral β-blockade was also found to reduce the rate of enlargement of abdominal aortic aneurysms in humans [16]. Furthermore, β-blockers decrease the sympathetic tone and increase the parasympathetic tone, thus improving autonomic imbalance. In our series, the positive influence of β-blocker therapy is reflected in a significantly lower increase of aortic diameter and a significantly lower incidence of dissection-related surgical intervention in chronic type B aortic dissection. Therefore, the presumptive benefits of β-blockers derive not only from their impact on blood pressure, but also from their negative inotropic and chronotropic properties. This is why some authorities do not recommend vasodilators without concomitant administration of a drug with negative inotropic and chronotropic effects. However, such an approach may actually increase the velocity of left ventricular contraction (dP/dt) and make the dissection worse. For the same reason, sublingual use of nifedipine is controversial; it reduces blood pressure in an uncontrolled fashion, potentially causing a reflex increase in heart rate and contractility, and thus, increasing the dP/dt [9].

Since serious early complications of type B dissection are not uncommon and unexpected late rupture (which is almost invariably fatal) cannot reliably be predicted, there has been an increasing tendency to operate on acute and subacute type B dissections [17]. The indication for emergency surgery after the acute phase of a type B aortic dissection must be balanced against the not inconsiderable morbidity and mortality rates carried by emergency surgery (Fig. 1). Although surgery is steadily improving, the risk is still quite substantial and there are few guidelines to suggest patients could justifiably be exposed to these surgical risks, apart from those with very large aneurysms or pronounced symptoms. Furthermore, it is known that age and chronic obstructive pulmonary disease are powerful predictors of rupture of chronic type B dissection [18,19]. It has been speculated that there must be a common, possibly smoking-related

defect in connective tissue metabolism that predisposes towards both lung and aortic pathology in susceptible persons. On the other hand, our series shows a good survival rate and a good rate of freedom from any event. The low hospitalization rate of patients treated strictly with β-blockers and the low treatment cost/patient per year are further reasons to encourage a positive view of a medical approach to type B aortic dissection which includes frequent treatment review, as well as regular determination of aortic diameter.

References

[1] Fuster V, Ip JH. Medical aspects of acute aortic dissection. Semin Thorac Cardiovasc Surg 1991;3:219–224.

[2] Rizzoli G, Scalia D, Casarotto D, Tiso E. Aortic dissection type A versus type B: a different post-surgical death hazard? Eur J Cardiothorac Surg 1997;12:202–208.

[3] Rossi-Foulkes R, Roman MJ, Rosen SE, Kramer-Fox R, Ehlers KH, O'Loughlin JE, Davis JG, Devereux RB. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. Am J Cardiol 1999;83:1364–1368.

[4] Halpern B, Char F, Murdoch J, Horton W, McKusick VA. A prospectus on the prevention of aortic rupture in the Marfan syndrome with data on survivorship without treatment. Johns Hopkins Med J 1971;129:123–129.

[5] Salim MA, Alpert BS, Ward JC, Pyeritz RE. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. Am J Cardiol 1994;74:629–633.

[6] Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome see comments. N Engl J Med 1994;330:1335–1341.

[7] Wheat WJ, Palmer R, Bartley T, Seelan R. Treatment of dissecting aneurysm of the aorta without surgery. J Thorac Cardiovasc Surg 1965;50:364–373.

[8] Marui A, Mochizuki T, Mitsui N, Koyama T, Kimura F, Horibe M. Toward the best treatment for uncomplicated patients with type B acute aortic dissection: a consideration for sound surgical indication. Circulation 1999;100:II275–II280.

[9] Razavi M. Acute dissection of the aorta: options for diagnostic imaging. Cleve Clin J Med 1995;62:360–365.

[10] Fuster V, Andrews P. Medical treatment of the aorta. Cardiol Clin 1999;17:697–715,viii.

[11] Yin FC, Brin KP, Ting CT, Pyeritz RE. Arterial hemodynamic indexes in Marfan's syndrome. Circulation 1989;79:854–862.

[12] Wheat Jr MW, Palmer RF. Dissecting aneurysms of the aorta. Curr Probl Surg 1971;1:43.

[13] Carney Jr WI, Rheinlander HF, Cleveland RJ. Control of acute aortic dissection. Surgery 1975;78:114–120.

[14] Simpson CF, Boucek RJ, Noble NL. Influence of D-, L-, and DL-propranolol, and practolol on beta-amino-propionitrile-induced aortic ruptures of turkeys. Toxicol Appl Pharmacol 1976;38:169–175.

[15] Beavan D, Murphey E. Dissecting aortic aneurysm during methonium therapy. Br Med J 1956;I:77–80.

[16] Leach SD, Toole AL, Stern H, DeNatale RW, Tilson MD. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. Arch Surg 1988;123:606–609.

[17] Juvonen T, Ergin MA, Galla JD, Lansman SL, McCullough JN, Nguyen K, Bodian CA, Ehrlich MP, Spielvogel D, Klein JJ, Griepp RB. Risk factors for rupture of chronic type B dissections. J Thorac Cardiovasc Surg 1999;117:776–786.

[18] Dapunt OE, Galla JD, Sadeghi AM, Lansman SL, Mezrow CK, de Asla RA, Quintana C, Wallenstein S, Ergin AM, Griepp RB. The natural history of thoracic aortic aneurysms. J Thorac Cardiovasc Surg 1994;107:1323–1332; Discussion pp. 1332–1333.

[19] Masuda Y, Yamada Z, Morooka N, Watanabe S, Inagaki Y. Prognosis of patients with medically treated aortic dissections. Circulation 1991;84:III7–III13.

Appendix A. Conference discussion

Dr C. Alhan (*Istanbul, Turkey*): Was there a contraindication for β-blocker usage in patients not using β-blockers? That's my first question.

Dr Genoni: We had only one patient with severe peripheral arterial disease who had contraindications to β-blockers. All other patients did not show signs of contraindication. And it's important to say that this is a retrospective study, so we had no chance to change their medical treatment in the follow-up time.

Dr Alhan: My second question is, did you look at the initial aortic diameter at the time of dissection? Was there a difference between the two groups?

Dr Genoni: No. The diameter is comparable for the two groups. The univariate analysis of our patients revealed that a diameter larger than 4.5 cm is a predictor for surgery in the follow-up and also for death. Based on these observations, the indications for surgery is a diameter of 4.5 cm.

Dr R. Ascione (*Bristol, UK*): I have a few questions to ask. First, did you actually control the blood pressure during your follow-up period?

Dr Genoni: Yes. The values of blood pressure are comparable for both groups.

Dr Ascione: Was the blood pressure controlled? I mean was it in the right range?

Dr Genoni: Yes, retrospectively with the questionnaire we sent to the patients.

Dr Ascione: If that's the case, I would like to ask you which is the underlying mechanism allowing the β-blockers to achieve this advantage?

Dr Genoni: Theoretically, the use of β-blockers offers many potential benefits: firstly a decrease of the blood pressure; then reduction of the pulsatile force (dP/dt); and finally, decreasing of the sympathetic tone. Around that, I think that the benefit of β-blockers derives not only from the direct impact of the blood pressure, but also from the negative inotropic and chronotropic properties.

Dr Ascione: So, we should then conclude that the most important thing is not controlling blood pressure. I mean this is the message we are getting.

Dr Genoni: I think both are very important. So, if you cannot control the blood pressure with β-blockers only, you need additional medication.

Dr A. Arbulu (*Detroit, MI, USA*): Your work confirms the suggestion of Dr Myron Wheat over 30 years ago.

Our experience is very similar to yours, and although those patients had antihypertensive therapy, you show that some of those came to surgery. In a very small series, we found that the control of the hypertension at home was not the same as it used to be while they were in the hospital. We were able to obtain this information from a group of visiting nurses. I wonder if you had, in your experience, any out-of-hospital follow-up?

Dr R. Griepp (*New York, NY, USA*): To the best of my knowledge, this is the first published account that β-blockers actually have a beneficial effect on the natural history of aortic disease in patients other than those with Marfan's syndrome. My first question is, whether you are aware of any other published accounts that show a beneficial effect of β-blockers per se?

My second question relates to your graph of freedom from adverse events after acute dissection; it appears that most of the benefit of the β-blockers occurs in the first year and that thereafter, the lines are parallel. Do you think that this phenomenon is real, does it mean we only need to use β-blockers in the first year or is this apparent concentration of the benefits in the first year an artefact of the study for which you have another explanation?

Dr Genoni: I don't know. Our results call for a very strict follow-up examination of the diameter of the aorta. Furthermore, it is mandatory for all patients to take β-blockers for the rest of their lives.

Dr M. Turina (*Zurich, Switzerland*): If I may add, that's the second conse-

quence of this paper. Probably the equally important one is the need for very strict follow-up in the first 2–4 years. Our incidence of adverse events, after 4 years, becomes flat, but in the first 4 years, this patient needs very careful follow-up, otherwise you will have a substantial mortality in this period, and this is the second message which Dr Genoni is bringing to you.

Dr R. Martinez (*Tenerife, Spain*): Do you use β-blockers in chronic bronchial disease?

Dr Genoni: If the patient tolerates the medication, we'll prescribe it. It depends on the patient.

Dr Turina: The question really is, do we know how many patients were put on β-blockers and had to be taken off? Do you have this data?

Dr Genoni: We had only one patient with a contraindication to β-blockers.